EMSO Madrid 2014

Modulation of the Immune Response in Breast Cancer: Dream or reality?

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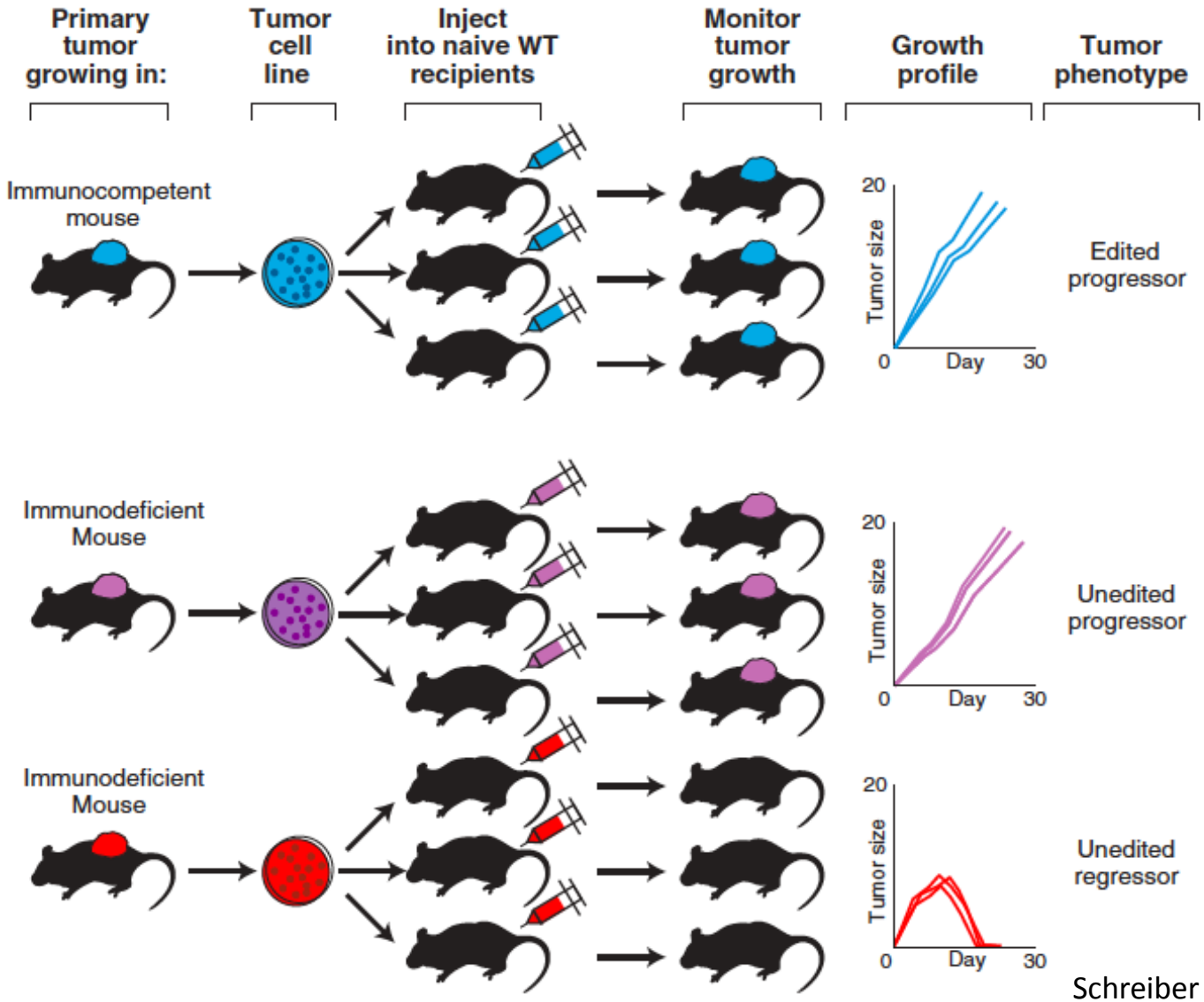
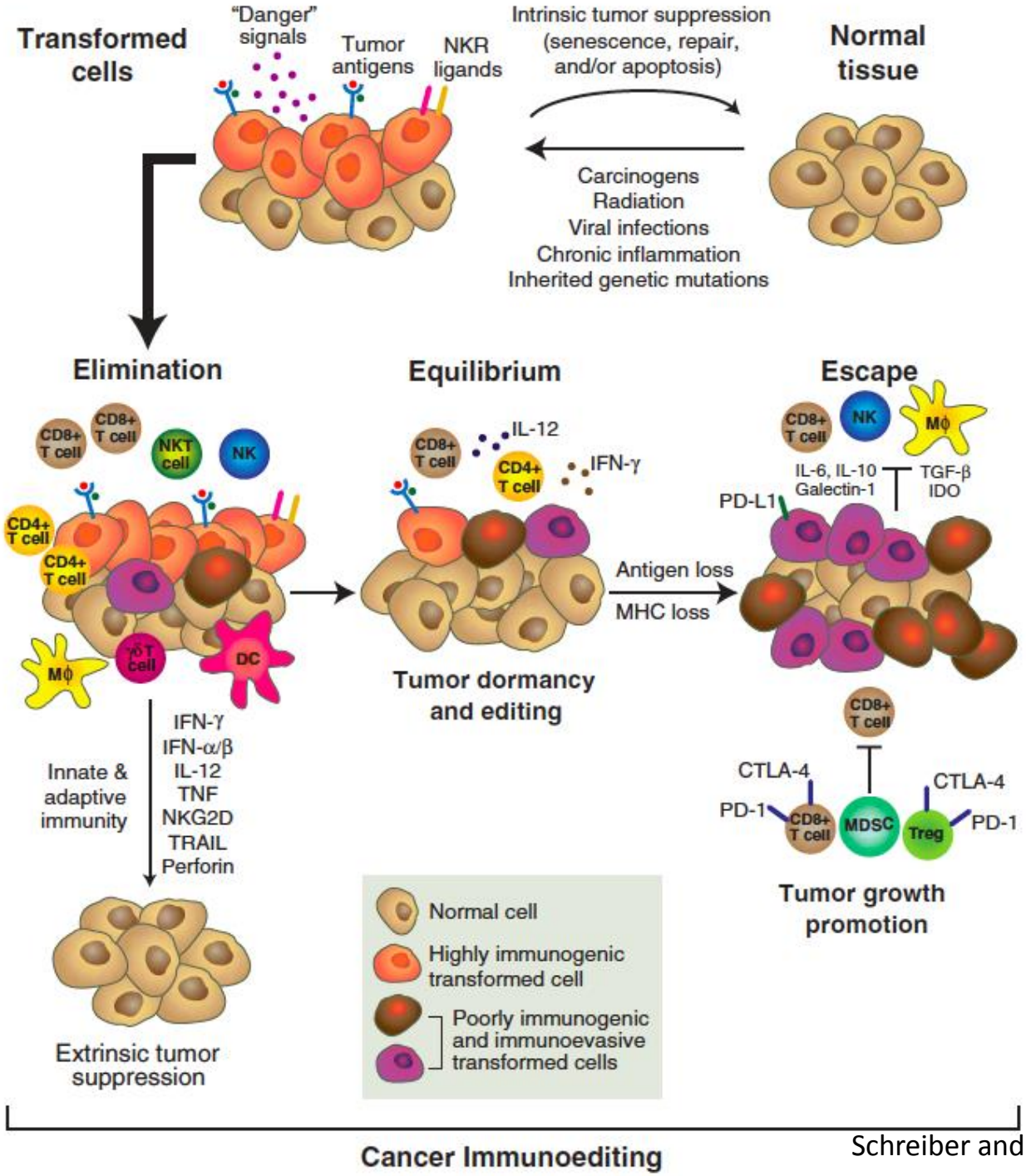
Evidence for Immunity in Cancer

- **Spontaneous tumor regressions (melanoma and lymphoma)**
- **Higher incidence of tumors in immunosuppressed, immunodeficient (AIDS) as well as older patients**
- **Regression of metastases after removal of primary tumor (renal cell ca)**
- **Lymphocyte infiltration of tumors and associations with prognosis**

Cancer immunoediting- elimination, equilibrium and escape



Schreiber and Smyth Science 2011

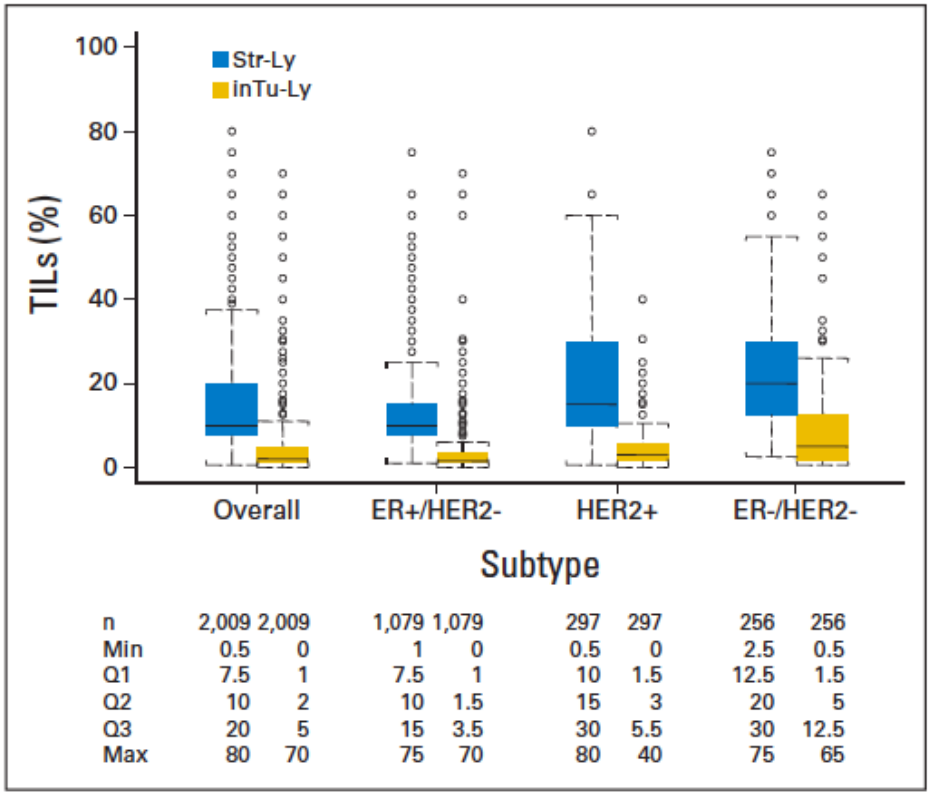


Schreiber and Smyth Science 2011

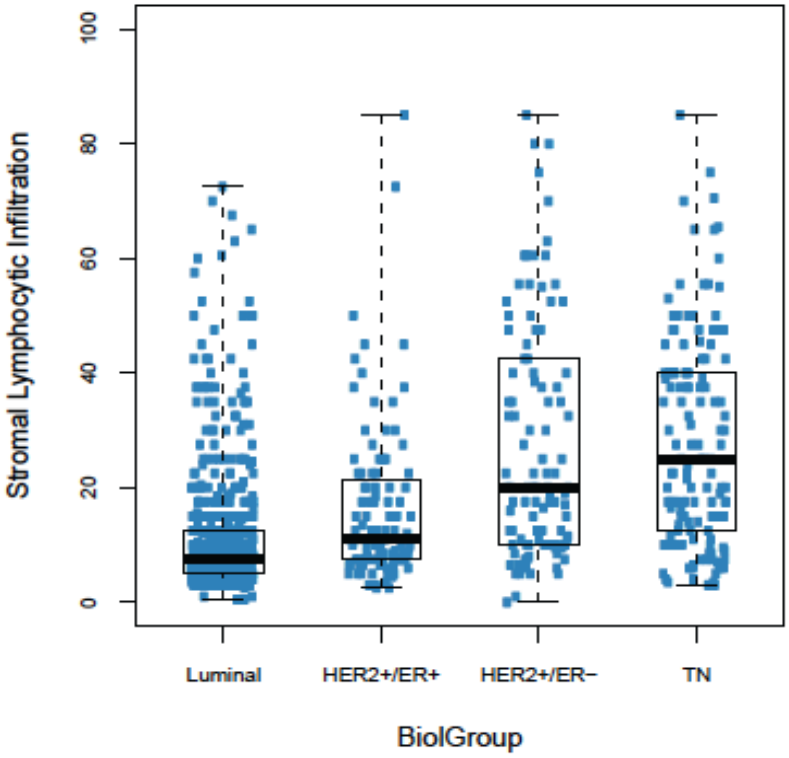
What's happening in breast cancer?

- **Tumor infiltrating lymphocytes (TILs) are seen in primary breast cancer**
- **Associated with a better prognosis in primary TNBC treated with anthracycline-based chemo**
- **Associated with a better prognosis in primary HER2+ BC treated with anti-HER2 therapy+chemo**

Higher levels in HER2+ and TNBC



n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65



n	591	103	106	134
Min	0.5	2.5	0	3
Q1	5	7.5	10	12.5
Q2	7.5	11	20	25
Q3	12.5	21.2	42.5	40
Max	72.5	85	85	85

Loi et al, JCO 2012; Ann Oncol 2014

Primary TNBC post adjuvant CT

Table 1. Recently Published Data on the Prognostic Value of TILs in Primary TNBC

Dataset	BIG 2-98	FinHER	ECOG 2197 and ECOG 1199	Post Neoadjuvant
Clinical trial dataset	Yes	Yes	Yes*	No
TILs evaluated before (at diagnosis) or after chemotherapy	Before	Before	Before	After
No. of patients with TNBC	256	145	481	278
Node positive, %	100	78.5	59	54
Median follow-up, years	8	5.2	10.6	6.3
Chemotherapy type	Anthracycline/taxane	Anthracycline/taxane/ vinorelbine	Anthracycline/taxane	Anthracycline/taxane
TILs				
Median %	20	25	10	15
IQR, %	12.5-30	12.5-40	10-20	10-30
Significant association with involved axillary LNs at diagnosis	No	Yes: more TILs, more LN+	Yes: more TILs, more LN+	NA
LPBC, %†	10.6	11.6	4.4	14.8
Stromal TILs (10%) HR (adjusted)				
DFS	0.85	0.82	0.84	NG
95% CI	0.74 to 0.98	0.67 to 0.99	0.74 to 0.95	
P	.025	.047‡	.005	
DDFS	NG	0.77	0.81	0.86
95% CI		0.61 to 0.98	0.68 to 0.97	0.77 to 0.96
P		.02	.02	.01
OS	0.83	0.81	0.79	0.86
95% CI	0.71 to 0.98	0.61 to 1.1	0.67 to 0.92	0.77 to 0.97
P	.023	.1	.003	.01

Loi et al, JCO 2014

What do TILs represent?

- **TILs represent pre-existing host anti-tumor immunity**
  - **The more the better**

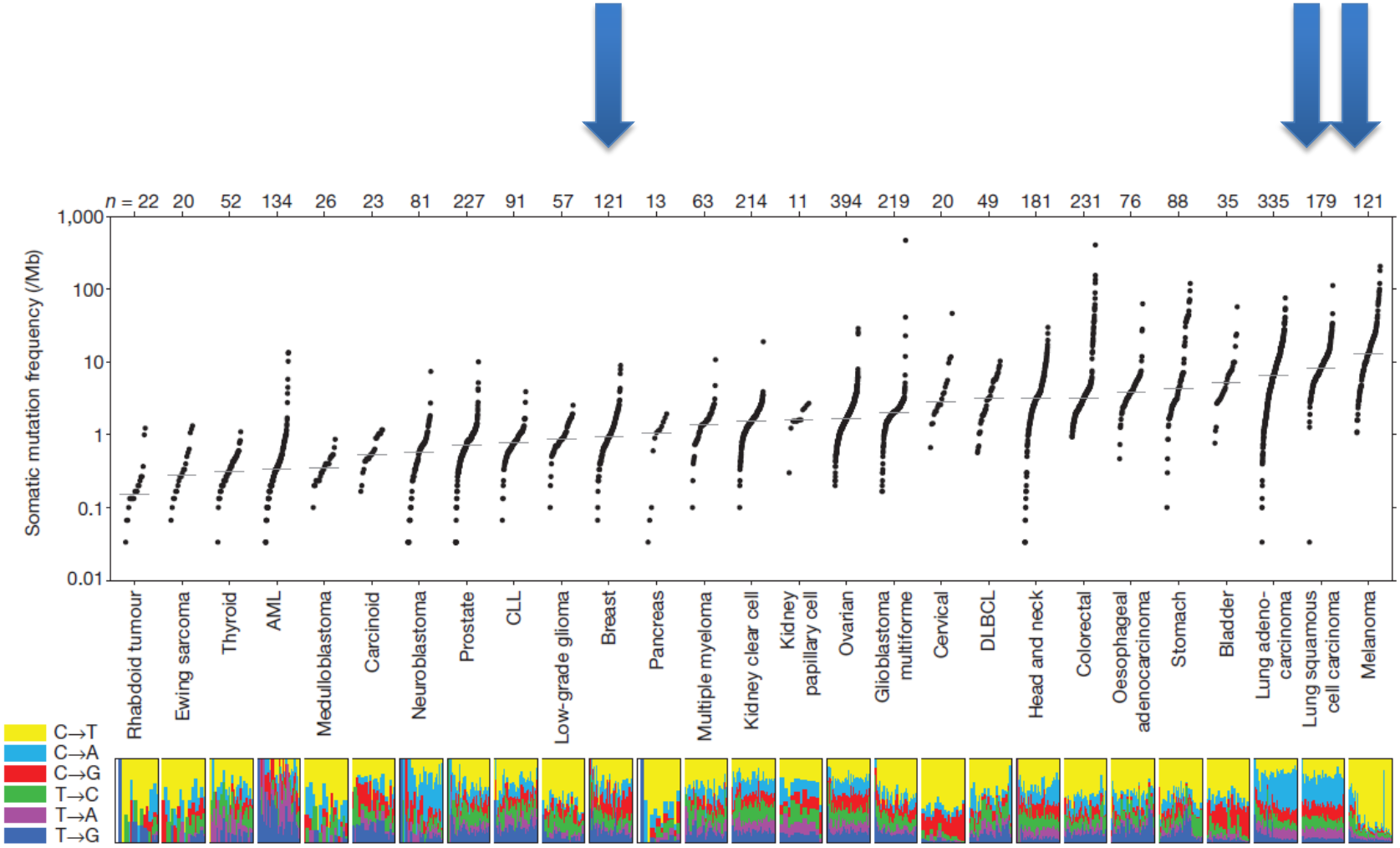
- **An activated immune response which has been terminated (naturally) or attenuated (tumor-mediated).**

FOR TNBC AND HER2+ BC, IMMUNE APPROACHES MAY BE ABLE TO IMPROVE DISEASE OUTCOMES.

Questions going forward in developing immune approaches in BC

- **Why do some patients have TILs in their tumor: pre-existing immunity?**
- **How can we enhance the immune response or create an immune response where none exists?**
- **Will TILs be a biomarker of response to T cell checkpoint inhibition (or other immunotherapies) or will we need PDL1+?**
- **Will T cell checkpoint inhibition be enough?**

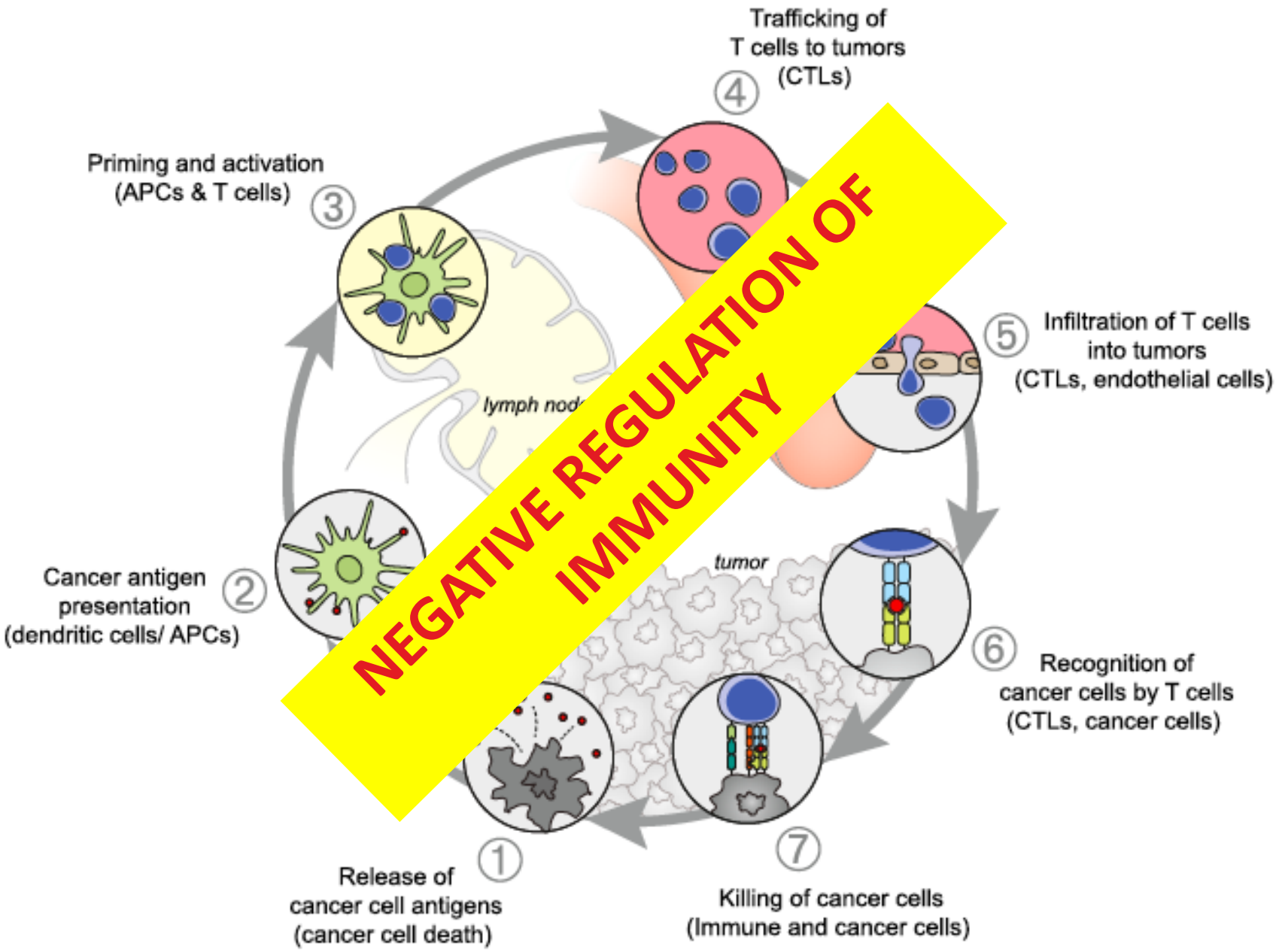
Mutations act as tumor antigens



Lawrence et al, Nature 2013

Immunogenic mutations in breast cancer

- **The spectrum of "immunogenic" peptides is yet to be described.**
- **TNBC have higher mutational load= higher TILs**
- **HER2+ also higher mutational load as well as overexpression of HER2 protein.**
- **BRCA1-mutated tumors classically associated with high TILs**

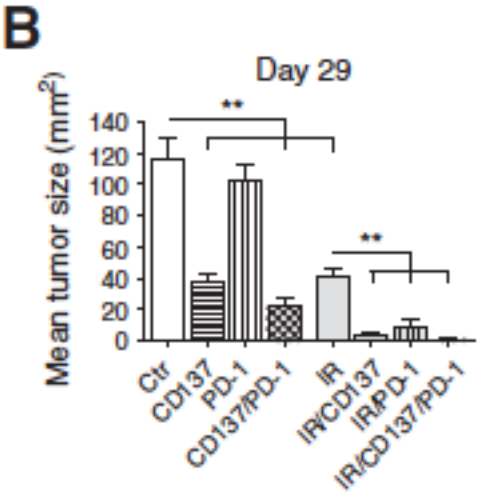


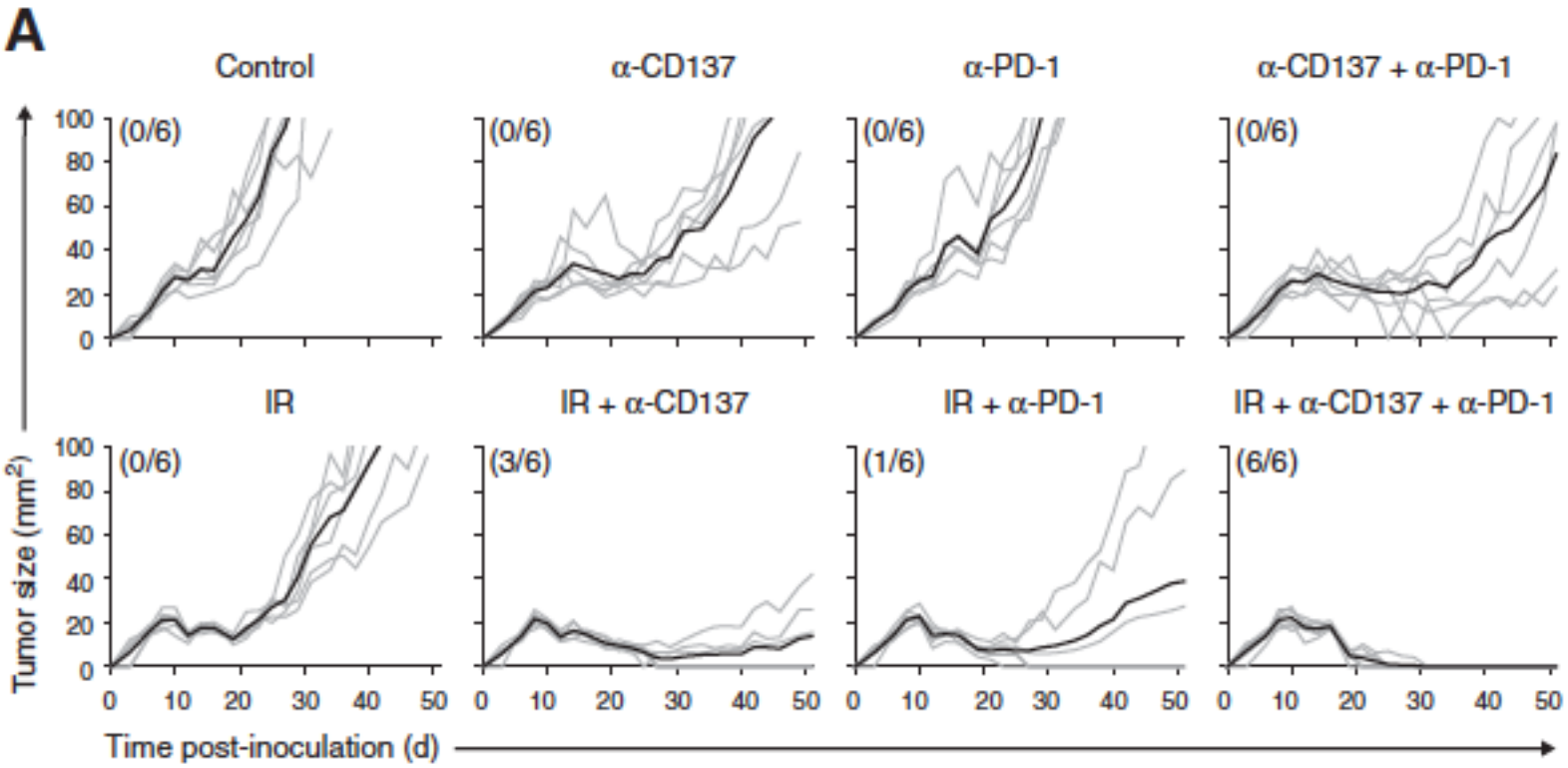
Chen and Mellman, Immunity 2012

Cancer Research

Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Immunomodulatory Antibodies

Inge Verbrugge, Jim Hagekyriakou, Leslie L. Sharp, et al.



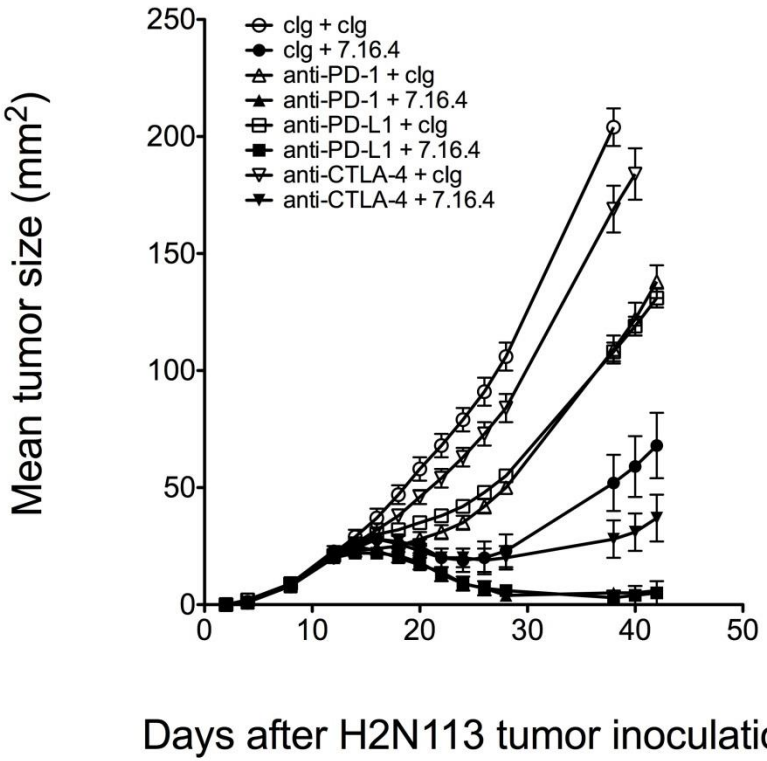


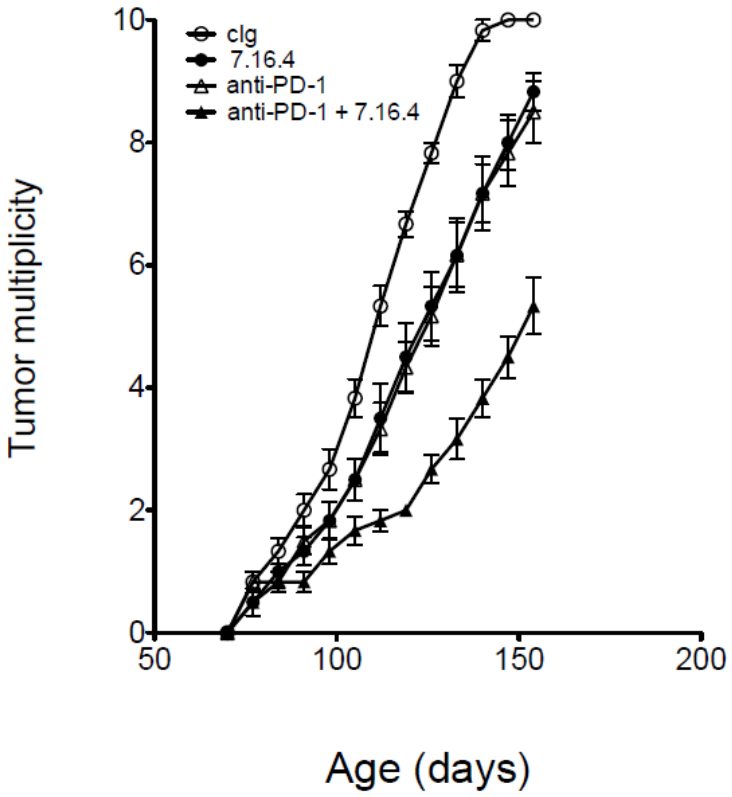
2010

BOSTON trial I/II

- **Pilot study of Stereotactic ablative radiotherapy (SABR) +/- anti-PD1- antibody**
- **Objective to assess safety and immune endpoints**
- **Population is oligo-metastatic breast cancer (1-3 mets).**

Augmenting T cell responses with trastuzumab





Background BALB/c MMTV/neu mice

Stagg et al, PNAS 2011

PANACEA trial: NCT02129556

IBCSG

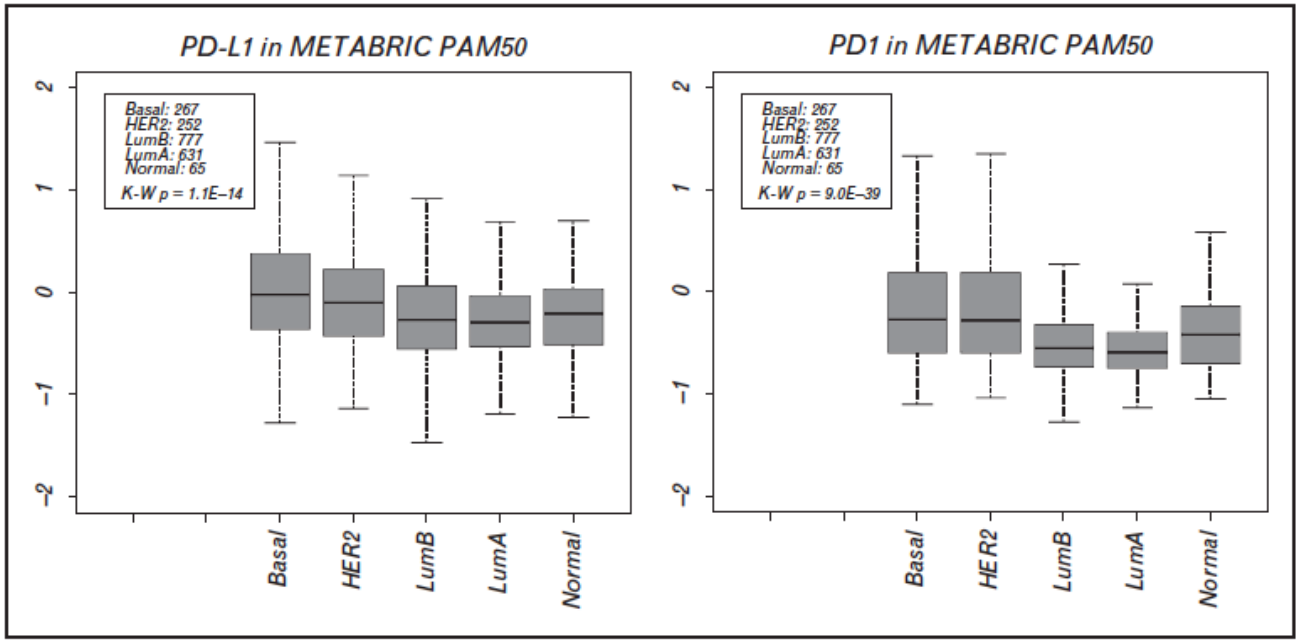
Phase Ib/II trial of anti-PD-1 monoclonal ANtibody in AdvanCed, Trastuzumab-resistant, HER2-positive breast cAncer

Primary Endpoint is efficacy of the combination

BIG
Breast International Group

Will TILs be a biomarker of response to T – cell checkpoint inhibition?

- **Correlation between TILs and T cell checkpoints.**
- **TILs per se may overcome issues of IHC (see guidelines paper by Salgado et al, Annals of Oncology)**
- **Pre-existing immunity is important**



Savas et al 2014

Other possibilities to enhance immunity

- **Will one immunotherapy be enough?**
  - **Blockade of additional checkpoints: PD1, PDL1, TIM-3 LAG3, VISTA etc (lots of T negative regulators)**
  - **Adenosine, IDO-1, ICOS, other immunosuppessive molecules**
  - **OX40, 41BB**

- **Standard BC therapies**
  - **Chemotherapies- gemcitabine, cisplatin**
  - **Targeted therapies-priming and cell death**
  - **Radiation**

Conclusions for immune modulation in breast cancer

- **There is correlative and preclinical data suggesting that immunotherapies will be effective for certain subtypes of BC**
  - **Await clinical trials**
- **Pre-existing immunity is present in some patients**
  - **Relief of negative regulation seems to be most important**
  - **TILs *per se* likely an appropriate biomarker for T cell checkpoint inhibition**
- **Will T cell checkpoint inhibition be enough?**
  - **Many std therapies likely synergistic.**
  - **Combinations of IT likely**

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